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Synthesis of Monoalkylated Calix[4]arenes via Direct Alkylation

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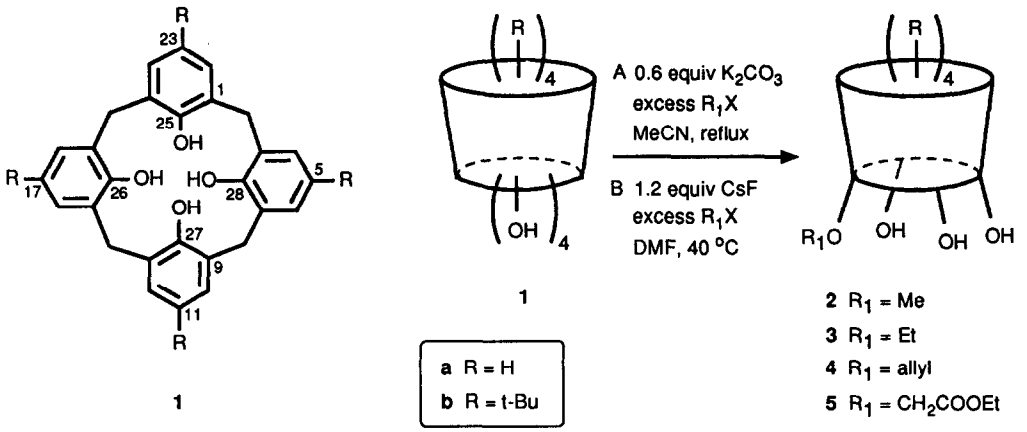
Abstract: *A new one-step procedure for the synthesis of monoalkylated calix[4]arenes is presented. Reaction of calix[4]arene* ***1a*** *or* ***1b*** *with 1.2 equivalent of a weak base (K_2CO_3 in MeCN or CsF in DMF) and excess of alkylating agent affords the monoalkylated calix[4]arenes in moderate to good yields.*

Calix[4]arenes (**1**) are versatile building blocks for molecules with different properties.[1] The increasing interest in these molecules is stimulated by the simple large-scale synthesis of the calix[4]arenes, and the different ways in which they can be functionalized selectively. General procedures have been developed for the *syn*-1,3-dialkylation[2] of the phenolic oxygen atoms (at the lower rim) and the 1,3-difunctionalization at the upper rim,[3] the *syn*-1,2-dialkylation at the lower rim,[4] and the *syn*-trialkylation at the lower rim[5] of calix[4]arenes. Examples of both *anti*-1,2- and *anti*-1,3-dialkylated calix[4]arenes[6,7] and of the two other isomers of trialkylated calix[4]arenes[7] have been published. All of them are obtained in reasonable yield in one- to three-step procedures that seem generally applicable. Until very recently only a few monoalkylated calix[4]arenes were known. They were obtained in low yield either via direct substitution[8,9] or via a three-step synthesis.[10] Recently, several monoalkyl ethers of calix[4]arenes, obtained via selective dealkylation of *syn*-1,3-di- or tetraalkylated calix[4]arenes, have been reported.[11] Direct monoalkylation of *p-tert*-butylcalix[4]arene **1b** with NaH as a base and 1 equiv of alkylating agent has been reported, but this reaction gives considerable amounts of disubstituted calix[4]arene as a byproduct.[5,7] In this paper we report a general one-step method for the monoalkylation of calix[4]arenes.



Scheme 1.

pK_a Measurements of calix[4]arenes have revealed that one proton is very acidic (a so-called super-acidic proton) and that a considerable gap exists between the pK_a values for the first and the second deprotonation step, which varies from 1.5 to 8.0 for different calix[4]arenes.[12] Therefore it is expected that the first deprotonation and alkylation step can be accomplished selectively if a weak base is used. Indeed, when calix[4]arene **1a** or **1b** is treated with 0.6 equiv of K_2CO_3 and excess of alkylating agent in refluxing acetonitrile (MeCN) (Method A), the monoalkylated calix[4]arenes are obtained in reasonable to good yields (Scheme 1, Table 1). However, in most of these reactions some *syn*-1,3-dialkylated calix[4]arene is still formed. When the reaction is carried out with 1.2 equiv of CsF[13] in dimethylformamide (DMF) at 40 °C (Method B) the monoalkylated calix[4]arenes are obtained in higher yields than in the K_2CO_3 reactions and with less of the *syn*-1,3-dialkylated calix[4]arenes as byproducts.

It seems strange that despite the considerable pK_a difference between the first and the second deprotonation step it is so difficult to obtain selectively the monoalkylated calix[4]arenes. However, in a recent publication, the pK_a values of *p-tert*-butylcalix[4]arene (**1b**) and its methyl ethers are estimated, and the results show that the pK_a values of **1b** and its monomethyl ether are of comparable magnitude, but that the pK_a values of the 1,3-di- and the trimethyl ether are > 5 pK_a units higher.[8] The monodeprotonation of a calix[4]arene is very easy because of the efficient stabilization of the monoanion by two hydrogen bonds from the neighboring phenol units. The second deprotonation is more difficult because the proton has to be abstracted from a *negatively charged* species and because in the resulting dianion every oxyanion can be stabilized by only one hydrogen bond. This shows in the gap between the pK_a values for the first and second deprotonation step of calix[4]arenes. When a proton is abstracted (at the diametrical position) from the *uncharged* monoalkyl ether the resulting anion will be stabilized by two hydrogen bonds, just like the calix[4]arene monoanion. Therefore, the pK_a values for a calix[4]arene and its monoalkyl ether are expected to be of comparable magnitude and this explains why even a weak base like K_2CO_3 (and $KHCO_3$ that is

Table 1. Yields of Monoalkylated Calix[4]arenes.

Compound	Method	Base	Solvent	Temperature (°C)	Time (h)	Yield (%)
2a	A	K_2CO_3	MeCN	reflux	50	58
2a	B	CsF	DMF	40	48	60
2b	A	K_2CO_3	MeCN	reflux	26	67
3a	A	K_2CO_3	MeCN	reflux	16	88
3b	A	K_2CO_3	MeCN	reflux	18	44
3b	B	CsF	DMF	40	16	65
4a	A	K_2CO_3	MeCN	reflux	16	37
4a	B	CsF	DMF	40	40	85
4b	A	K_2CO_3	MeCN	reflux	17	47
5b	A	K_2CO_3	MeCN	reflux	24	61
5b	B	CsF	DMF	40	16	75

formed during the reaction) cannot completely discriminate between the first and the second deprotonation step (i.e., deprotonation of the unsubstituted and of the monoalkylated calix[4]arene, respectively). The strength of the base F^- is not exactly known. However, it is generally considered to form a very strong hydrogen bond with an acidic proton rather than affecting complete deprotonation.[13] Our results seem to indicate that this makes a difference for the relative reactivities of the unsubstituted and the monoalkylated calix[4]arenes.

Deprotonation of a 1,3-dialkylated calix[4]arene will be relatively difficult, because the resulting oxyanion cannot be stabilized by a hydrogen bond, or only by a fairly weak one from the diametrical OH group. This explains why the alkylation of calix[4]arenes is so easily stopped at the 1,3-dialkylated stage.

The procedure presented for the monoalkylation of calix[4]arenes gives yields that are comparable to those obtained via the two-step procedure published earlier.[11] Its advantages are that only one reaction step is involved and that a wider range of alkylating agents can be used, including the ester reagents that lead to compound **5b** and analogous compounds.

EXPERIMENTAL

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard. All chemicals were reagent grade and used without further purification. Compounds **1a**[10] and **1b**[14] were prepared according to the literature. Acetonitrile was dried over molecular sieves (3 Å). Dimethylformamide (DMF) was distilled and kept over molecular sieves (4 Å). Dichloromethane and chloroform were distilled before use. Petroleum ether refers to the fraction boiling at 40-60 °C and was distilled before use. Chromatographic separations were performed on silica gel 60 (SiO_2, E. Merck, particle size 0.040-0.063 mm, 230-400 mesh). The presence of CH_2Cl_2 or $CHCl_3$ in the analytical samples was confirmed by ^1H NMR spectra of the samples in $CDCl_3$ or CD_2Cl_2, respectively.

General procedures for monoalkylation of calix[4]arenes.

Method A. A suspension of calix[4]arene **1a** (0.15 g, 0.35 mmol) or *p-tert*-butylcalix[4]arene **1b** (toluene complex, 0.25 g, 0.38 mmol), and K_2CO_3 (0.03 g, 0.20 mmol) in acetonitrile (10 mL) was stirred at reflux temperature for 0.5 h. The alkylating agent (3.5 mmol) was added and the reaction mixture was stirred for 16-50 h. After cooling the solvent was removed under reduced pressure. The remaining solid was taken up in CH_2Cl_2 (50 mL) and washed with 1 N HCl (2 x 50 mL) and water (50 mL). The organic layer was dried over $MgSO_4$ and evaporated to give a crude product. This contained in most cases some *syn*-1,3-disubstituted calix[4]arene as well as unsubstituted calix[4]arene. The latter was for a large part removed by taking up the crude product in ethyl acetate and filtering off the unsubstituted calix[4]arene. After evaporation of the solvent the product was purified by column chromatography.

Method B. To a solution of CsF (0.18 g, 1.2 mmol) in dry DMF (20 mL) were added calix[4]arene **1a** or *p-tert*-butylcalix[4]arene **1b** (toluene complex) (1 mmol), and the alkylating agent (10 mmol). The reaction mixture was stirred at 40 °C for 16-48 h. The progress of the reaction was followed by TLC and after completion the reaction was quenched with 2 N HCl (40 mL). The reaction mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with water (2 x 25 mL) and dried with $MgSO_4$. After evaporation of the solvent the remaining crude product was taken up in CH_2Cl_2/MeOH (1 : 1). This solution was filtered (to remove unreacted calix[4]arene), after which it was left standing so that the product could crystallize.

As alkylating agents the bromides were used, except for R_1 = Et, Me for which the iodides were used. Reaction times and yields for all reactions are given in Table 1.

28-Methoxycalix[4]arene (2a). Method A, eluent CH_2Cl_2/petroleum ether 3 : 1; mp 276-277 °C (lit.[11] 276-277 °C ($CHCl_3$/MeOH)).

Method B, purification by column chromatography (CH_2Cl_2/hexane 1 : 1); mp 275-276 °C.

28-Methoxy-*p-tert*-butylcalix[4]arene (2b). Method A, eluent CH_2Cl_2/petroleum ether 3 : 1; mp 206-208 °C (lit.[11] 203-204 °C ($CHCl_3$/MeOH)).

28-Ethoxycalix[4]arene (3a). Method A, eluent CH_2Cl_2/petroleum ether 1 : 1; mp 295-298 °C; ^{1}H NMR δ 9.79 (s, 1 H, OH), 9.42 (s, 2 H, OH), 7.15-7.0 (m, 8 H, *m*-ArH), 6.91 (t, 1 H, J = 7.5 Hz, *p*-ArH), 6.75-6.65 (m, 3 H, *p*-ArH), 4.45, 4.31 (d, 2 H, J = 13.4 Hz, $ArCH_2Ar$ ax), 4.23 (q, 2 H, J = 7.5 Hz, OCH_2), 3.45 (d, 4 H, J = 13.4 Hz, $ArCH_2Ar$ eq), 1.75 (t, 3 H, J = 7.5 Hz, CH_3); ^{13}C NMR δ 151.1 (s, ArC-OR_1), 150.5, 149.2 (s, ArC-OH), 72.5 (t, OCH_2), 31.7, 31.3 (d, $ArCH_2Ar$), 15.1 (q, CH_3); mass spectrum, *m/e* 452.198 (M^+, calcd 452.199). Anal. Calcd for $C_{30}H_{28}O_4 \cdot 0.2CH_2Cl_2$: C, 77.6; H, 6.12. Found: C, 77.7; H, 5.84.

28-Ethoxy-*p-tert*-butylcalix[4]arene (3b). Method A, eluent CH_2Cl_2/petroleum ether 1 : 1; mp 206-208 °C (lit.[11] 200-201 °C (MeOH)). Method B; mp 200-201 °C (CH_2Cl_2/MeOH).

28-(2-Propenyloxy)calix[4]arene (4a). Method A, eluent CH_2Cl_2/petroleum ether 1 : 1; mp 207-209 °C ($CHCl_3$/MeOH) (lit.[11] 216-217 °C).

Method B; the crystallized product contained some *syn*-1,3-disubstituted calix[4]arene that was removed via column chromatography (hexane/ethyl acetate 9 : 1); mp 205-207 °C.

28-(2-Propenyloxy)-*p-tert*-butylcalix[4]arene (4b). Method A, eluent CH_2Cl_2/petroleum ether 1 : 1; mp 273-275 °C ($CHCl_3$/MeOH); ^1H NMR δ 10.17 (s, 1 H, OH), 9.50 (s, 2 H, OH), 7.10, 7.04 (s, 2 H, ArH), 7.05 and 6.98 (ABq, 4 H, J = 2.4 Hz, ArH), 6.55-6.35 (m, 1 H, =CH), 5.64 (d, 1 H, J = 17.2 Hz, =CH*H*), 5.51 (d, 1 H, J = 10.2 Hz, =CH*H*), 4.67 (d, 2 H, J = 6.3 Hz, OCH_2), 4.37 (d, 2 H, J = 12.9 Hz, $ArCH_2Ar$ ax), 4.27 (d, 2 H, J = 13.6 Hz, $ArCH_2Ar$ ax), 3.43 (d, 4 H, J = 13.4 Hz, $ArCH_2Ar$ eq), 1.22, 1.20 (s, 9 H, $C(CH_3)_3$), 1.21 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 149.1 (s, ArC-OR_1), 148.4, 147.8 (s, ArC-OH), 126.4 (d, =CH), 120.3 (t, $=CH_2$), 77.6 (t, OCH_2), 34.2, 34.0, 33.9 (s, $C(CH_3)_3$), 33.0, 32.3 (t, $ArCH_2Ar$), 31.4, 31.2 (q, $C(CH_3)_3$); mass spectrum, *m/e* 688.448 (M^+, calcd 688.449). Anal. Calcd for $C_{47}H_{60}O_4 \cdot 0.2CHCl_3$: C, 79.8; H, 8.55. Found: C, 79.7; H, 8.51.

2-[(*p-tert*-Butylcalix[4]arene-28-yl)oxy]acetic acid, ethyl ester (5b). Method A, eluent CH_2Cl_2/ petroleum ether 3 : 1; mp 275-276 °C.

Method B; mp 264-266 °C dec (CH_2Cl_2/MeOH).

^1H NMR δ 10.23 (s, 1 H, OH), 9.26 (s, 2 H, OH), 7.09, 7.05 (s, 2 H, ArH), 7.04, 6.98 (d, 2 H, J = 2.3 Hz, ArH), 4.89 (s, 2 H, OCH_2COOR), 4.48, 4.30 (d, 2 H, J = 13.4 Hz, $ArCH_2Ar$ ax), 4.41 (q, 2 H, J = 7.2 Hz, OCH_2), 3.43 (d, 4 H, J = 13.4 Hz, $ArCH_2Ar$ eq), 1.41 (t, 3 H, J = 7.2 Hz, CH_3), 1.23, 1.19 (s, 9 H, $C(CH_3)_3$), 1.20 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 169.5 (s, C=O), 149.9 (s, ArC-OR_1), 148.2 (s, ArC-OH), 72.0 (t, OCH_2COOR), 61.9 (t, OCH_2CH_3), 34.2, 34.0, 33.9 (s, $C(CH_3)_3$), 33.0, 32.5 ($ArCH_2Ar$), 31.5, 31.4, 31.2 (q, $C(CH_3)_3$), 14.2 (q, CH_3); mass spectrum, *m/e* 734.443 (M^+, calcd 734.455). Anal. Calcd for $C_{48}H_{62}O_6 \cdot 0.2CH_2Cl_2$: C, 77.1; H, 8.37. Found: C, 76.7; H, 8.59.

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2. Until now an adequate nomenclature for the exact conformation of a calix[4]arene is missing. In this paper we use the prefix syn to indicate that two large O-substituents (that cannot rotate through the annulus) are on the same face of the molecule and the prefix anti when two large O-substituents are on different faces of the molecule. The numbers 1-4 indicate the four phenyl rings of the calix[4]arene in sequential order. The IUPAC name for the calix[4]arene moiety (**1a**) is pentacyclo-[19.3.1.^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetraol.
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